Refinements in the etiology and management of penile squamous cell carcinoma

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SUMMARY

Epidemiological and etiological factors of penile carcinoma are described in **chapter 1,** with the emphasis on the role of human papillomavirus (HPV). High-risk HPV types are causally involved in the pathogenesis of carcinomas of the anogenital tract, particularly cervical carcinomas whereas the role of HPV in penile cancer is less clear. High risk HPV's exert their oncogenic effect by expressing the oncoproteins E6 and E7, which bind to and inactivate the p53 and Rb tumor suppressor gene products, respectively. The introduction also provides an overview of diagnostic tools and treatment options of penile carcinoma. **Chapter 2** provides a comprehensive analysis of 53 penile carcinomas which was performed to determine which mechanisms might be involved in the disruption of the $p16^{INK4A}$/cyclin D/Rb pathway. This pathway plays an important role in cell cycle control. To that end HPV presence, $p16^{INK4A}$ expression, promoter methylation and expression of the BMI-1 polycomb gene product were studied. Sixteen (30%) of the 53 carcinomas were found to harbor high-risk HPV DNA, 15 of which contained HPV 16. HPV 16 E6/E7 oncogene transcripts were detected in 13 (87%) of the 15 HPV 16 containing carcinomas. Strong immunostaining of $p16^{INK4A}$ was significantly more frequent in carcinomas with high-risk HPV DNA ($P<0.001$) and amongst those with HPV 16 DNA, it was more frequent in cases with E6/E7 transcripts ($P=0.029$). This supports an active role of HPV E7 in interfering with the $p16^{INK4A}$/cyclin D/Rb pathway. Methylation of the $p16^{INK4A}$ promoter and overexpression of the BMI-1 polycomb gene product may provide alternative modes of interference with this pathway. These phenomena were mutually exclusive and found in the absence of HPV in 15% and 10% of the penile carcinomas respectively. So, there seem to exist at least 3 plausible mechanisms by which the $p16^{INK4A}$/cyclinD/Rb pathway can become disrupted during penile carcinogenesis, one of which is mediated by high-risk human papilloma virus. In **chapter 3** the prevalence of high-risk HPV was examined in a large series of penile squamous cell carcinomas (SCCs). Also the relationship between HPV and survival was assessed. Specimens of 171 patients with penile carcinoma were tested for high-risk HPV DNA presence by GP5+/6+-PCR. High-risk HPV DNA was detected in 29% of the tumors, with HPV 16 being the predominant type,

accounting for 76% of high-risk HPV containing SCCs. Disease-specific 5-years survival in the high-risk HPV negative group and high-risk HPV positive group was 78% and 93%, respectively (P=0.03). In multivariate analysis, the HPV status was an independent predictor for disease-specific mortality (P=0.017) with a hazard ratio of 0.21 (95% CI: 0.06-0.76). These results indicate that the presence of high-risk HPV (29%) confers a survival advantage in patients with penile carcinoma. **Chapter 4** analyses the accuracy of physical examination and imaging in assessing the extent of the primary tumor in squamous cell carcinoma of the penis. The extent of the primary tumor determines whether the patient is a candidate for penis conserving treatment and also has prognostic value. Physical examination, ultrasonography and magnetic resonance imaging (MRI) were performed pre-operatively in 33 patients. Comparing clinical and pathological measurements, tumor size was assessed most accurately by physical examination (residual standard deviation (SD) of 8.1mm). Ultrasonography and MRI were less precise (residual SD: 8.9mm and 9.3mm). Regarding infiltration depth, ultrasonography and MRI showed comparable accuracy (residual SD: 3.7mm and 3.8mm). Positive predictive value of corpus cavernosum infiltration was 100% for physical examination, 67% for ultrasonography and 75% for MRI. Therefore, physical examination remains the most reliable method for estimation of tumor size and corpus cavernosum infiltration. Ultrasonography is the first choice of imaging to determine infiltration depth, if this remains unclear after physical examination. MRI shows similar results compared to ultrasonography but is far more expensive. **Chapter 5** provides our experience with primary tumor treatment in T1 and T2 penile squamous cell carcinoma. The 5-year local recurrence-free estimate after penis conservation was similar for T1 and T2 tumors (P=0.1) and overall 63% (95% CI: 54%-72%) compared to 88% (95% CI: 81-95%) for partial amputation (P=0.0003). In case of a local recurrence after penis conserving treatment, local control could be achieved in 94% (51/54) of cases. Nine of 10 patients with a local recurrence after partial amputation of the penis died of disease.

In patients with T1 tumors treated with penis conservation, 33% (7/21) of patients with local recurrences developed regional recurrences compared to only 6% (3/47) of patients without local recurrences (P=0.005). Of the patients with T2 tumors treated with penis conservation, 27% (9/33) of patients with local recurrences developed regional recurrences compared to 22% (12/56) of patients without local recurrences (P=0.56). As the time to a regional recurrence is similar for patients with and without local recurrences and the inguinal recurrences rate is not increased in patients with local recurrences when the inguinal regions are pathologically staged (merely T2 tumors), it seems that local recurrences are not the focus of regional recurrences. However, a local recurrence can be used as a portender of lymphatic regional spread in cases without pathological staging of the inguinal regions (merely T1 tumors). In **chapter 6**, we analyzed clinical, morphological and immunohistochemical features of sarcomatoid penile carcinoma. Of 341 patients treated in our insitute, five had sarcomatoid penile carcinoma (1.4%). Four of five patients developed distant metastatic disease and died within one year after diagnosis. Diagnosis was mainly based on the expression of keratin filaments in a predominantly spindle cell penile tumor or by the identification of carcinomatous and sarcomatoid areas in H&E stained slides of the primary tumor. Thus, sarcomatoid squamous cell carcinoma of the penis appears to be an aggressive subtype of penile carcinoma. **Chapter 7** deals with the clinical implications of dynamic sentinel node biopsy in patients with penile carcinoma. A total number of 90 clinically node-negative patients were prospectively studied. Preoperative lymphoscintigraphy was performed after intradermal injection of ^{99m}Tc-nanocolloid around the primary tumor. The sentinel node was intraoperatively identified with the aid of intradermal administered patent blue dye and a gamma-ray detection probe. Histopathological examination of sentinel nodes included serial sectioning and immunohistochemical staining. Regional lymph node dissection was performed only if metastasis was found in a sentinel node. Lymphoscintigraphy visualized 217 sentinel nodes in 159 inguinal regions of 88 patients. A total of 208 sentinel nodes were intraoperatively identified in 149 inguinal regions of 88 patients. Sentinel

node metastasis was found in 19 inguinal regions of 18 patients. Four of 8 patients with unilateral clinically N1 stage had a tumor-positive sentinel node at the opposite site. During a median follow-up of 36 months (range 5-95), regional recurrence after excision of a tumor-negative sentinel node or after non-visualization was seen in five patients, resulting in a false-negative rate of 22% (5/23). Three-year disease specific survival was 98% and 71% for patients with a tumor-negative or tumor-positive sentinel node respectively (P= 0.0018). This study shows that occult lymph node metastases in penile cancer can be detected with a sensitivity of about 80% by lymphatic mapping and sentinel node biopsy. His approach allows for early lymph node dissection in most lymph node positive patients and provides important prognostic information. Lymph node-negative patients can be prevented from substantial morbidity associated with elective lymphadenectomy.

Chapter 8 evaluates clinical outcome of clinically node-negative penile carcinoma managed by surveillance or further diagnosed by dynamic sentinel node biopsy with subsequent resection of lymph node metastases. From 1956-1994, 85 patients with primary T2-3N0M0 penile squamous cell carcinoma were managed by initial surveillance of the regional lymph nodes while from 1994 until 2001, 68 patients underwent dynamic sentinel node biopsy. While both populations were similar for prognostic factors as patient age, clinical T-stage, tumor grade, presence of vascular invasion and infiltration depth disease-specific three-year survival in the surveillance group was 79% and 91% in the sentinel node group (P=0.04). Thus, early detection of lymph node metastases by dynamic sentinel node biopsy and subsequent resection in clinically node-negative T2-3 penile carcinoma improves survival in comparison with a wait and see policy. In **chapter 9** pathological parameters of inguinal lymph node involvement were identified which were predictive of pelvic lymph node involvement and survival. Tumor grade of the involved inguinal lymph nodes (OR: 6.0 (CI 95%: 1.2-30.3)) and the number of involved nodes (≤2 vs. >2) (OR: 12.1 (CI 95%: 3.0-48.1)) were independent prognostic factors for pelvic lymph node involvement. Extra-capsular growth (OR: 2.3 (CI 95%: 1.1-4.8)), bilateral inguinal involvement (OR: 3.4 (CI 95% 1.2-9.4)) and pelvic lymph

node involvement (OR: 3.1 (CI 95%: 1.4-6.6)) were independent prognostic factors for disease-specific survival. Conclusively, patients with only one or two inguinal lymph nodes involved without extra-capsular growth and no poorly differentiated tumor within these nodes are at low risk of pelvic lymph node involvement and have good prognosis with a five year survival rate of about 90%. A pelvic lymph node dissection seems to be unnecessary in these cases. **Chapter 10** provides the conlusions of this thesis and a general discussion. New imaging techniques are described for identification of occult lymph node metastases. Genetic analysis of the primary tumor might enable us in the near future to predict the clinical course of the disease for each individual patient.